High-Dose Methylprednisolone Has No Benefit Over Moderate Dose for the Correction of Tetralogy of Fallot

Keski-Nisula, Juho

2016-09

Keski-Nisula , J , Pesonen , E , Olkkola , K T , Ahlroth , T , Puntila , J , Andersson , S , Neuvonen , P J & Suominen , P K 2016 , ' High-Dose Methylprednisolone Has No Benefit Over Moderate Dose for the Correction of Tetralogy of Fallot ' , Annals of Thoracic Surgery , vol. 102 , no. 3 , pp. 870-876 . https://doi.org/10.1016/j.athoracsur.2016.02.089

http://hdl.handle.net/10138/224570
https://doi.org/10.1016/j.athoracsur.2016.02.089

publishedVersion

High-Dose Methylprednisolone Has No Benefit Over Moderate Dose for the Correction of Tetralogy of Fallot

Juho Keski-Nisula, MD, Eero Pesonen, MD, PhD, Klaus T. Olkkola, MD, PhD, Terri Ahlroth, RN, Juha Puntila, MD, Sture Andersson, MD, PhD, Pertti J. Neuvonen, MD, PhD, and Pertti K. Suominen, MD, PhD

Department of Anesthesia and Intensive Care, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki; Department of Anesthesiology, Intensive Care, and Pain Medicine, Meilahti Hospital, University of Helsinki and Helsinki University Hospital, Helsinki; Department of Anesthesiology, Intensive Care, Emergency Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki; Department of Pediatric Surgery, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki; Department of Neonatal Intensive Care, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki; and Department of Clinical Pharmacology, University of Helsinki and HUSLAB, Helsinki University Hospital, Helsinki, Finland

Background. **The optimal dose of methylprednisolone during pediatric open heart surgical procedures is unknown. This study compared the antiinflammatory and cardioprotective effects of high and lower doses of methylprednisolone in children undergoing cardiac operations.**

Methods. **Thirty children, between 1 and 18 months old and undergoing total correction of tetralogy of Fallot, were randomized in double-blind fashion to receive either 5 or 30 mg/kg of intravenous methylprednisolone after anesthesia induction. Plasma concentrations of methylprednisolone, interleukin-6 (IL-6), IL-8, and IL-10, troponin T, and glucose were measured at anesthesia induction before administration of the study drug, at 30 minutes on cardiopulmonary bypass (CPB), just after weaning from CPB, and at 6 hours after CPB. Troponin T and blood glucose were also measured on the first postoperative morning.**

Results. **Significantly higher methylprednisolone concentrations were measured in patients receiving 30 mg/kg of methylprednisolone at 30 minutes on CBP, after weaning from CPB and at 6 hours after CPB ($p < 0.001$). No differences were detected in IL-6, IL-8, IL-10, or troponin concentrations at any time point. Blood glucose levels were significantly higher in patients receiving 30 mg/kg of methylprednisolone at 6 hours after CPB ($p = 0.04$) and on the first postoperative morning ($p = 0.02$).**

Conclusions. **Based on the measured concentrations of interleukins or troponin T, a 30 mg/kg dose of methylprednisolone during pediatric open heart operations does not offer any additional antiinflammatory or cardioprotective benefit over a 5 mg/kg dose. Higher dose of methylprednisolone exposes patients more frequently to hyperglycemia.**

(Ann Thorac Surg 2016;102:870–6)

The antiinflammatory effect of corticosteroids during pediatric open heart surgical procedures was substantiated in several studies [1–4]. Although some randomized studies reported that corticosteroids reduced perioperative troponin release, the clinically meaningful cardioprotective effect is questionable [5–8]. In addition, the effect on clinical outcome after pediatric heart operations is controversial. The use of steroids has been associated with improved hemodynamics and shortened duration of postoperative mechanical ventilation and intensive care stay [9, 10]. Conversely, steroids have been noted to increase morbidity, especially in lower-risk pediatric cardiac patients, and previous studies showed a possible association of steroids with increased number of infections, hyperglycemia, and possible perioperative renal dysfunction [4, 8, 11–13].

The protocols of steroid administration vary among different pediatric cardiac centers [14, 15]. According to an international survey the two most common practices of administration are a single dose of steroid either at the induction of anesthesia or perioperatively in the cardiopulmonary bypass (CPB) prime [14]. We noted in a recent study that methylprednisolone (MP) administration at anesthesia induction was more effective for antiinflammatory purposes than administration in the CPB circuit [9]. Both administration routes decreased troponin T levels at the same extent but exposed patients to hyperglycemia compared with placebo.

In the present study we compared a single dose of 30 mg/kg of preoperative intravenous MP with a dose of 5 mg/kg of MP in children between 1 and 18 months old who were undergoing primary surgical total correction of

Accepted for publication Feb 25, 2016.

Address correspondence to Dr Keski-Nisula, Department of Anesthesia and Intensive Care, Children's Hospital, Helsinki University Hospital, PO Box 281, Stenbäckinkatu 11, FI-00029 HUS, Helsinki, Finland; email: juho.keski-nisula@hus.fi.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.02.089

tetralogy of Fallot. Our hypothesis was that administration of 30 mg/kg of MP at anesthesia induction would lead to significantly higher plasma concentrations of MP and produce better antiinflammatory and cardioprotective effect than 5 mg/kg of MP.

Patients and Methods

Ethics and Informed Consent

The study protocol was approved by the Ethics Committee of Helsinki University Hospital and also by the Finnish Medicines Agency. It was registered in the European Union Drug Regulating Authorities Clinical Trials (Eudra-CT 2008-007413-76). Written informed consent was obtained from the parents of each participating study patient before the study commenced.

Study Design

This randomized (sealed envelope), double-blind study included 30 patients, between 1 and 18 months of age who were having total correction of tetralogy of Fallot. Exclusion criteria were as follows: prematurity, defined as gestational age of less than 36 weeks; previous cardiac surgical procedures; and preoperative steroid treatment. After anesthesia induction, placement of the arterial line, and collection of the first study plasma sample, patients were randomized to receive either 5 or 30 mg/kg of intravenous MP. A pharmacist who was not involved in the care of these patients prepared the MP solutions. The syringes of the study drug were covered with nontransparent paper foil. According the study protocol, no additional perioperative steroids were given to study patients.

Intraoperative Management

Balanced anesthesia was attained with sufentanil, pancuronium, propofol or (S)-ketamine, and sevoflurane. Myocardial protection and CBP were accomplished by using the methods described previously [16]. Patients received 30 mL/kg of cold blood cardioplegia after aortic cross-clamp, and 10 mL/kg of cardioplegia was then administered every 20 minutes. Terminal tepid cardioplegia was administered before declamping of the aorta. Because of prolonged study patient recruitment time, the cardioplegia administration protocol changed in our department during the study period. The 6 last patients (3 in each study group) received a 2-minute infusion of cold (24°C) blood cardioplegia, mixed at a ratio of 1:1 (blood to cardioplegia) during aortic cross-clamp, and thereafter, a 1-minute infusion of cold blood cardioplegia was administered every 20 minutes. Terminal tepid cardioplegia was not administered to these patients. Approximately 4 mg/kg of sodium heparin was used for anticoagulation before CPB, and the Hepcon HMS Plus Hemostasis Management System (Medtronic, Minneapolis, MN) was used to obtain the target heparin concentration of 6 units/mL during CPB. Protamine sulfate was used to reverse the anticoagulant effect of heparin after patients were weaned from CPB. All the study patients received a bolus of 30,000 KIU/kg (4.2 mg/kg) of aprotinin before CPB and a continuous infusion of 30,000 KIU/kg/h (4.2 mg/kg/h) during CPB.

Inotropes and Insulin

Milrinone was used for all patients as the first-line inotropic drug. Epinephrine and norepinephrine were added to milrinone for hemodynamic support when needed. Five patients (1 patient in the 5 mg/kg MP group and 4 patients in the 30 mg/kg MP group) received perioperative phenylephrine because of cyanotic spells. Levosimendan was used for 1 patient in the 5 mg/kg MP group and for 2 patients in the 30 mg/kg MP group. Insulin was administered in the pediatric intensive care unit (PICU) as deemed necessary by the clinician in charge. In general, insulin infusion was started when blood glucose concentrations were greater than 12 mmol/L in two consecutive measurements.

Blood Samples

In this study, 5 mL of arterial blood was collected into tubes containing sodium citrate at four different time points: T1, after anesthesia induction before administration of MP; T2, 30 minutes after initiation of CPB; T3, 5 minutes after administration of protamine; and T4, 6 hours after cessation of CPB. Plasma was separated immediately by centrifugation and was stored at −70°C until analysis. Interleukin-6 (IL-6), IL-8, and IL-10 were determined at time points T1 to T4 by using commercial enzyme-linked immunosorbent assay kits (Quantikine, R&D Systems, Abington, United Kingdom). Total plasma concentration of MP was determined at time points T2 to T4 by using a high-performance liquid chromatography–electrospray–tandem mass spectrometry method [17]. The lower limit of MP quantification was 2 ng/mL, and the interday coefficient of variation was less than 10%. Troponin T concentrations were determined using an electrochemiluminescence immunoassay (Elecsys 2010 immunoanalyzer, Roche Diagnostics, Berlin, Germany) at time points T1, T3, and T4 and at 6 o'clock on the first postoperative morning. Blood glucose was collected for study purposes at time points T1, T2, T3, and T4 and at 6 o'clock on the first postoperative morning.

Statistical Analysis

Plasma concentrations of MP, IL-6, IL-8, IL-10, and troponin T were used as primary outcome measures. Blood glucose level served as a secondary outcome measure. Pertinent physiologic and clinical parameters were also collected and analyzed even though they were not study endpoints. Calculations of previous study data indicated that 12 patients would be required to demonstrate a 20% difference in IL-6 values between the two study groups ($\alpha = 0.05$, $1\text{-}\beta = 0.8$) [3]. Fifteen patients were enrolled in both study groups to compensate for possible dropouts. One dropout in the MP 5 mg/kg group occurred because of cancellation of the operation after randomization.

Data were analysed using GraphPad Prism 5.0a for Macintosh (GraphPad Software, La Jolla, CA). Plasma concentrations of cytokines and troponin were not

normally distributed; thus, we used the Mann-Whitney U test for the comparisons between the groups. The χ^2 test was used for comparison of frequencies between the two groups; p values less than 0.05 were considered to be statistically significant. Data are expressed as medians and interquartile range.

Results

Demographic data with no significant differences are presented in Table 1. Significantly higher mean MP concentrations ($p < 0.001$) were measured at every time point T2, T3, and T4 in patients who received intravenous MP 30 mg/kg compared with the dose of 5 mg/kg (Fig 1). However, no significant differences were observed between the study groups in concentrations of inflammatory interleukins IL-6 ($p = 0.59$ to 0.95) and IL-8 ($p = 0.45$ to 0.91) or in the levels of antiinflammatory IL-10 ($p = 0.37$ to 0.68) at any of the time points (Fig 2). Moreover, the troponin T levels of both study groups were similar at all the measured time points ($p = 0.38$ to 0.98) (Fig 3). Administration of 30 mg/kg of MP resulted in higher blood glucose concentrations at 6 hours after CPB ($p = 0.04$) and on the first postoperative morning ($p = 0.02$) (Fig 1). Four patients in the MP 30 mg/kg group received insulin versus none in the MP 5 mg/kg group ($p = 0.04$). Seven patients in the MP 30 mg/kg group received amiodarone infusion because of postoperative junctional ectopic tachycardia or atrial tachycardia versus 2 patients in the MP 5 mg/kg group ($p = 0.06$).

The postoperative laboratory and clinical data are presented in Table 2. No significant differences were found for postoperative lactate levels, central venous saturation, inotropic score, or levels of N-terminal pro–B-type natriuretic peptide (NT-proBNP). The postoperative blood leukocyte count was similar for both groups. Two cases of postoperative infection, one case of pneumonia, and one case of mediastinitis occurred in the MP 30 mg/kg group. The duration of mechanical ventilation or PICU stay did not differ between the groups. One patient in the MP 5 mg/kg group needed postoperative extracorporeal life support during 6 days because of severe tricuspid valve leakage, unstable hemodynamics, and poor respiratory function. The patient was weaned form extracorporeal life support and recovered successfully. No deaths occurred during the 30-day follow-up period.

Comment

Administration of intravenous 30 mg/kg MP after anesthesia induction produced remarkably higher drug concentrations than did 5 mg/kg of MP. Even so, no benefit for antiinflammatory, cardioprotective, or clinical outcome was found. Patients who received high-dose MP had more hyperglycemia and concomitant need for insulin therapy. Our results discourage the use of high-dose 30 mg/kg MP and endorse the use of lower MP doses with equal antiinflammatory and possible cardioprotective effects and a lower incidence of hyperglycemia.

Despite producing adverse effects, high-dose steroid administration is common during pediatric cardiac surgical procedures [14, 15]. The complex nongenomic and genomic mechanisms of glucocorticoids in antiinflammatory action are still under discussion. Classically the therapeutic antiinflammatory effect of steroids has been described to be mediated through genomic transrepression of genes encoding inflammatory mediators. In transrepression, steroid-activated glucocorticoid receptor interferes with the activity of proinflammatory transcription factors, such as activator protein 1 (AP-1) and nuclear

Table 1. Patient Demographic Data (N = 29)[a]

Characteristics	MP 5 mg/kg (n = 14)	MP 30 mg/kg (n = 15)	*p* Value
Age (months)	5.8 (3.6, 8.6)	5.3 (4.2, 9.0)	0.71
Weight (kg)	7.0 (5.4, 8.3)	7.2 (6.1, 8.7)	0.57
Male/female (n)	8/6	8/7	…
Syndrome (n)	3	4	…
Down	2	3	…
Pierre Robin	…	1	…
CATCH-22	1	…	…
Preoperative β-blocker for cyanotic spells (n)	6	6	…
CPB support time (min)	99 (79, 107)	95 (79, 122)	0.75
Aortic cross-clamp time (min)	62 (52,80)	60 (51, 89)	0.68
Lowest temperature (°C)	32.0 (32.0, 34.0)	32.0 (31.7,34.0)	0.92
Surgical correction			
Transannular patch (n)	7	7	…
Valve-sparing surgery (n)	7	8	…
Primary sternal closure (n)	13	14	…
Late repeat sternotomy (n)	1	1	…

[a] Values are medians and interquartile range.

CPB = cardiopulmonary bypass; MP = methylprednisolone.

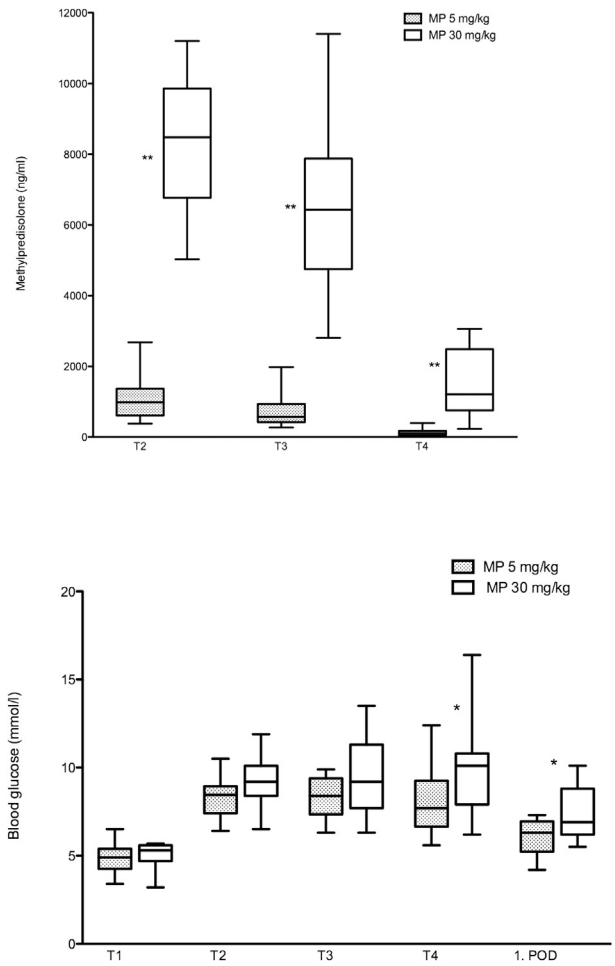

Fig 1. Plasma concentrations (median, interquartile range) of methylprednisolone (MP) and blood glucose in the MP 30 mg/kg and MP 5 mg/kg groups at different time points: T1, after anesthesia induction before administration of MP; T2, 30 minutes after initiation of cardiopulmonary bypass; T3, 5 minutes after protamine administration; T4, 6 hours after cessation of cardiopulmonary bypass; and 1. POD, on the first postoperative morning. Statistically significant differences are marked with one asterisk for $p < 0.05$ and with two asterisks for $p < 0.0001$.

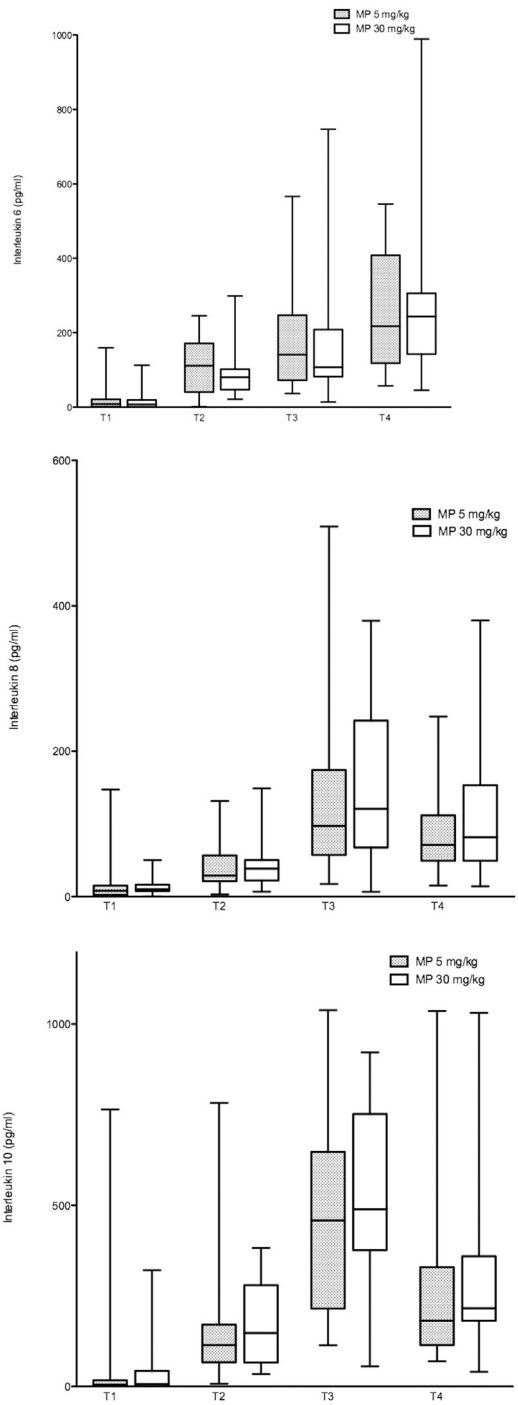

Fig 2. Plasma concentrations (median, interquartile range) of interleukin-6 (IL-6), IL-8, and IL-10 in the methylprednisolone (MP) 30 mg/kg and MP 5 mg/kg groups at different time points: T1, after anesthesia induction before administration of MP; T2, 30 minutes after initiation of cardiopulmonary bypass; T3, 5 minutes after protamine administration; and T4, 6 hours after cessation of cardiopulmonary bypass. No statistically significant ($p < 0.05$) differences were noted in concentrations between the groups.

factor κB (NF-κB), and leads to down-regulation of proinflammatory protein synthesis [18]. More recently, investigators have also noted that transactivation plays an essential role in the antiinflammatory action of steroids [18, 19]. In transactivation, the dimerized glucocorticoid receptor-protein complex binds to the promoter of glucocorticoid-regulated genes, thus inducing the expression of specific antiinflammatory genes and proteins such as NF-κB inhibitor, dual-specificity phosphatase (DUSP) 1, IL-10, glucocorticoid-induced leucine zipper (GILZ), and Annexin A1 [18]. Transactivation is also largely responsible for glucocorticoid metabolic and adverse effects as a result of enhanced expression of genes involved in metabolic processes [20]. In addition, investigators have noted that inhibition of AP-1 and NF-κB activities and the antiinflammatory effect is produced by much lower glucocorticoid concentration than is transactivation [21]. This action may at least partly explain the increased adverse effects with higher corticosteroid doses. Notably,

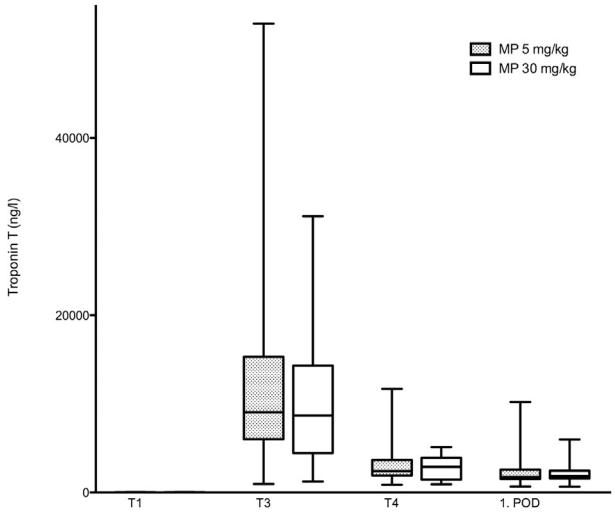

Fig 3. Plasma concentrations (median, interquartile range) of troponin T in the methylprednisolone (MP) 30 mg/kg and MP 5 mg/kg groups at different time points: T1, after anesthesia induction before administration of MP; T3, 5 minutes after protamine administration; T4, 6 hours after cessation of cardiopulmonary bypass; and 1. POD, on the first postoperative morning. No statistically significant ($p < 0.05$) differences were noted in concentrations of troponin T between the groups.

the MP concentrations after high-dose administration in our study remained higher at 6 hours after CPB than did the measured peak concentration in the lower-dose group that may prolong the existence of unwanted side effects such as hyperglycemia (Fig 1).

A previous study in pediatric cardiac patients compared the antiinflammatory effect of a single high dose of 30 mg/kg MP before CPB to with a single low dose of 2 mg/kg MP [2]. In accordance with our study, no beneficial antiinflammatory effect was demonstrated with high-dose steroid use in the study of Varan and colleagues [2]. Although the present study was not placebo controlled, the antiinflammatory effect of glucocorticoids during pediatric open heart operations has been demonstrated in previous studies [1, 4, 7, 8]. The preoperative administration during anesthesia induction has been noted to be more effective for antiinflammatory purposes than the intraoperative administration in CPB prime solution [8]. In a study by Graham and associates [13] in neonates undergoing cardiac surgical procedures, the combined preoperative and perioperative administration of 30 mg/kg of MP decreased the levels of IL-6 compared with a single preoperative administration. Nonetheless, the combined administration of MP did not improve the clinical outcome. In that study the two-dose MP regimen was associated with higher serum creatinine values and poorer postoperative diuresis [13].

Corticosteroids induce hyperglycemia by several mechanisms, and hyperglycemia becomes more frequent with increasing doses and longer duration of treatment. Corticosteroids increase the endogenous glucose production by activating genes involved in hepatic gluconeogenesis [22]. These drugs also enhance the effects of glucagon and epinephrine, thereby further increasing the synthesis of endogenous glucose. Corticosteroids also reduce peripheral glucose uptake by causing insulin resistance of the muscular and other peripheral tissues. Depending on dose and duration of treatment, corticosteroids also inhibit insulin production and secretion from pancreatic β cells [22]. In randomized clinical trials, tight glycemic control (blood glucose 4.4 to 6.1 mmol/L) did not reduce the rate of infections, mortality rate, length of stay, measures of organ failure, or need for mechanical

Table 2. Laboratory and Clinical Data (N = 29)

Characteristics	MP 5 mg/kg (n = 14)	MP 30 mg/kg (n = 15)	*p* Value
Arrival to intensive care unit			
Lactate (mmol/L)	1.25 (0.1, 1.7)	1.5 (1.2, 1.8)	0.31
White blood cell count (E^9/L)	10.5 (9.8, 13.8)	11.2 (10.2, 12.1)	0.93
Rectal temperature (°C)	35.9 (35.5, 36.4)	36.0 (35.2, 36.3)	0.76
Inotropic score	16.0 (11.5, 23.6)	23.3 (16.7, 26.3)	0.12
Central venous saturation (%)	60.4 (39.0, 69.6)	61.3 (53.5, 73.4)	0.44
First postoperative day[a]			
Lactate (mmol/L)	1.1 (0.9, 1.5)	1.2 (0.9, 1.6)	0.78
White blood cell count (E^9/L)	13.5 (11.7, 15.7)	13.4 (10.8, 15.7)	0.97
Rectal temperature (°C)	37.5 (37.4, 37.9)	37.4 (37.1, 37.7)	0.09
Inotropic score	5.1 (5.0, 7.6)	6.9 (5.1, 13.0)	0.11
Central venous saturation (%)	63.4 (61.6, 6.9)	61.5 (52.9, 71.5)	0.48
NT-proBNP	7,161 (4,990, 11,248)	7,221 (4,491, 8,765)	0.71
Ventilatory treatment (days)	1.1 (0.5, 1.5)	1.2 (0.8, 3.3)	0.36
Intensive care unit stay (days)	2.5 (2.0, 4.0)	4.0 (2.0, 7.0)	0.19

[a] Measured on the first postoperative day at 6:00 hours, except the inotropic score was calculated at 12:00 hours. Values are medians and interquartile range.

MP = methylprednisolone; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

ventilation compared with standard care after pediatric cardiac operations [23, 24]. Nonetheless, hyperglycemia has been associated with several detrimental effects in critically ill children. Vlasselaers and associates [25] noted that targeting of blood glucose to age-adjusted normal fasting concentrations improves short-term outcome of patients in the PICU. Faustino and Apkon [26] detected that hyperglycemia is frequent in patients in the PICU and is associated with greater hospital mortality rates and increased length of stay. Yates and colleagues [27] reported in a retrospective study that hyperglycemia is associated with increased organ dysfunction, infection, duration of ventilator treatment, PICU and hospital stay, and mortality rates in small children after cardiac operations. Moreover, in a retrospective cohort by Tala and associates [28], hyperglycemia was associated with increased venous thromboembolism in patients in the PICU. Because 30 mg/kg of MP produced hyperglycemia frequently but did not improve the clinical outcome, the use of higher MP doses cannot be recommended.

Administration of corticosteroids during pediatric open heart operations transiently decreases troponin release compared with placebo [5–8]. The possible cardioprotective effect may arise from the nonnuclear effect of corticosteroids on activation of endothelial-derived nitric oxide synthase (eNOS) that is associated with antiischemic properties [29]. In addition, because it is fast, the maximal activation of eNOS is probably achieved with a much lower steroid dose than an intravenous dose of 30 mg/kg of MP [8, 29]. In the present study no differences in troponin levels between the 30 and 5 mg/kg MP groups were noted. Although our study was limited by not measuring cardiac output with echocardiography, no differences were noted in indirect cardiac output measurements such as inotropic score, central venous saturation, or lactate levels. In transgenic mouse models, investigators observed that although normal signaling of glucocorticoid receptor in cardiomyocytes is crucial for the normal development and function of the heart, overexpression of both glucocorticoid and mineralocorticoid receptor activation in cardiomyocytes presents an increased risk of arrhythmias such as atrioventricular block, bradycardia, or increased occurrence of ventricular arrhythmias [30]. In our study 7 patients in the MP 30 mg/kg group received amiodarone infusion because of junctional ectopic tachycardia or atrial tachycardia compared with 2 patients in the MP 5 mg/kg group. However, this difference was not statistically significant. The results from our study and the finding that abnormally high glucocorticoid activity may in theory be detrimental for normal heart function do not support the administration of high doses of steroids for cardioprotective reasons.

We measured plasma MP concentrations previously in two series of children undergoing CPB [4, 8]. In the present study, the weight of the patients with tetralogy of Fallot was comparable to the weight of the previous patients with ventricular or atrioventricular septal defects [8]. Consequently, administration 30 mg/kg of MP also resulted in comparable mean total plasma MP concentrations [8]. On the contrary, the measured mean peak plasma concentrations of MP with similar administration were almost twice as high as in neonates, in whom the CPB prime volume is relatively high compared with body surface area [4]. It is evident that the measured MP plasma concentrations vary during CPB depending on the patient's size and the relative proportion of CPB prime volume to the patient's body surface area. Moreover, in our previous studies the standard weight-based dosing produced remarkable individual variability in plasma corticosteroid concentrations [4, 8]. Therefore, more studies and possibly the use of population pharmacokinetic methods are needed to optimize the dose of glucocorticoids during pediatric open heart operations.

Although the antiinflammatory effect of corticosteroids was demonstrated in earlier studies, the lack of a placebo group can be considered a limitation of the present study. Because of the relatively small sample size, there is a theoretical possibility for a type II error in data analyses. The cardioplegia protocol changed during the study period, and this change may also have influenced cardioprotection and troponin values. Conversely, the new protocol was used in equal number of patients in both study groups. The lack of echocardiographic cardiac output data can also be regarded as a limitation of the study. Nevertheless, we observed no differences in indirect cardiac output measurements or inotropic score.

In conclusion, despite producing significantly higher plasma MP concentrations, the administration of 30 mg/kg of MP at anesthesia induction was not superior in terms of antiinflammatory or cardioprotective action compared with 5 mg/kg of MP. Conversely, the high-dose administration exposed patients to postoperative hyperglycemia. The results from the present study discourage the use of 30 mg/kg of MP during pediatric open heart surgical procedures.

This work was financially supported by Helsinki University Hospital. The authors wish to thank the staff of the Children's Hospital and the children's parents for their contribution to this study.

References

1. Bronicki RA, Backer CL, Baden HP, Mavroudis C, Crawford SE, Green TP. Dexamethasone reduces the inflammatory response to cardiopulmonary bypass in children. Ann Thorac Surg 2000;69:1490–5.
2. Varan B, Tokel K, Mercan S, Dönmez A, Aslamaci S. Systemic inflammatory response related to cardiopulmonary bypass and its modification by methylprednisolone: high dose versus low dose. Pediatr Cardiol 2002;23:437–41.
3. Schroeder VA, Pearl JM, Schwartz SM, Shanley TP, Manning PB, Nelson DP. Combined steroid treatment for congenital heart surgery improves oxygen delivery and reduces postbypass inflammatory mediator expression. Circulation 2003;107:2823–8.
4. Keski-Nisula J, Suominen PK, Neuvonen PJ, et al. Methylprednisolone in neonatal cardiac surgery: reduced inflammation without improved clinical outcome. Ann Thorac Surg 2013;95:2126–32.
5. Checchia PA, Backer CL, Bronicki RA, et al. Dexamethasone reduces postoperative troponin levels in children

undergoing cardiopulmonary bypass. Crit Care Med 2003;31:1742–5.
6. Malagon I, Hogenbirk K, van Pelt J, Hazekamp MG, Bovill JG. Effect of dexamethasone on postoperative cardiac troponin T production in pediatric cardiac surgery. Intensive Care Med 2005;31:1420–6.
7. Heying R, Wehage E, Schumacher K, et al. Dexamethasone pretreatment provides anti- inflammatory and myocardial protection in neonatal arterial switch operation. Ann Thorac Surg 2012;93:869–76.
8. Keski-Nisula J, Suominen PK, Olkkola KT, et al. The effect of timing and route of methylprednisolone administration during pediatric cardiac surgery. Ann Thorac Surg 2014;99:180–5.
9. Ando M, Park IS, Wada N, Takahashi Y. Steroid supplementation: a legitimate pharmacotherapy after neonatal open heart surgery. Ann Thorac Surg 2005;80:1672–8.
10. Clarizia NA, Manlhiot C, Schwartz SM, et al. Improved outcomes associated with intraoperative steroid use in high-risk pediatric cardiac surgery. Ann Thorac Surg 2011;91:1222–7.
11. Pasquali SK, Hall M, Li JS, et al. Corticosteroids and outcome in children undergoing congenital heart surgery: analysis of the Pediatric Health Information Systems database. Circulation 2010;122:2123–30.
12. Pasquali SK, Li JS, He X, et al. Perioperative methylprednisolone and outcome in neonates undergoing heart surgery. Pediatrics 2012;129:385–91.
13. Graham EM, Atz AM, Butts RJ, et al. Standardized preoperative corticosteroid treatment in neonates undergoing cardiac surgery: results from a randomized trial. J Thorac Cardiovasc Surg 2011;142:1523–9.
14. Checcia PA, Bronicki RA, Costello JM, Nelson DP. Steroid use before pediatric cardiac operations using cardiopulmonary bypass: an international survey of 36 centers. Pediatr Crit Care Med 2005;6:441–4.
15. Robertson-Malt S, Afrane B, El Barbary M. Prophylactic steroids for pediatric open heart surgery. Cochrane Database Syst Rev 2007;(4):CD005550.
16. Suominen PK, Keski-Nisula J, Tynkkynen P, Kantoluoto S, Olkkola KT, Mildh L. The effect of tepid amino acid enriched induction cardioplegia on the outcome of infants undergoing cardiac surgery. Perfusion 2012;27:338–44.
17. Dodds HM, Taylor PJ, Cannell GR, Pond SM. A high-performance liquid chromatography–electrospray–tandem mass spectrometry analysis of cortisol and metabolites in placental perfusate. Anal Biochem 1997;247:342–7.
18. Spies CM, Strehl C, van der Goes MC, Bijlsma JWJ, Buttgereit F. Glucocorticoids. Best Pract Res Clin Rheumatol 2011;25:891–900.
19. Hübner S, Dejager L, Libert C, Tuckermann JP. The glucocorticoid receptor in inflammatory processes: transrepression is not enough. Biol Chem 2015;396:1223–31.
20. Jiang CL, Liu L, Li Z, Buttgereit F. The novel strategy of glucocorticoid drug development via targeting nongenomic mechanisms. Steroids 2015;102:27–31.
21. Roumestan C, Gougat C, Jaffuel D, Mathieu M. Glucocorticoids and their receptor: mechanism of action and clinical implications. Rev Med Interne 2004;25:636–47; [in French].
22. Perez A, Jansen-Chaparro S, Saigi I, Bernal-Lopez MR, Minambres I, Comez-Huelgas R. Glucocorticoid-induced hyperglycemia. J Diabetes 2014;6:9–20.
23. Agus MSD, Steil GM, Wypij D, et al. Tight glycemic control versus standard care after pediatric cardiac surgery. N Engl J Med 2012;13:1208–19.
24. Macrae D, Grieve R, Allen E, et al. A randomized trial of hyperglycemic control in pediatric intensive care. N Engl J Med 2014;370:107–18.
25. Vlasselaers D, Milants I, Demet L. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547–56.
26. Faustino EVS, Apkon M. Persistent hyperglycemia in critically ill children. J Pediatr 2005;146:30–4.
27. Yates AR, Dyke PC, Taeed R, et al. Hyperglycemia is a marker for poor outcome in the postoperative pediatric cardiac patient. Pediatr Crit Care Med 2006;7:351–5.
28. Tala JA, Silva CT, Pemira S, Vidal E, Faustino EVS. Blood glucose as a marker of venous thromboembolism in critically ill children. J Thromb Haemost 2014;12:891–6.
29. Hafezi-Moghadam A, Simoncini T, Yang Z, et al. Acute cardiovascular protective effects of corticosteroids are mediated by non-transcriptional activation of endothelial nitric oxide synthase. Nat Med 2002;8:473–9.
30. Oakley RH, Cidlowski JA. Glucocorticoid signaling in the heart: a cardiomyocyte perspective. J Steroid Biochem Mol Biol 2015;153:27–34.